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Subchronic Inhalation Toxicology of Ethylene Glycol Monoethyl Ether in the Rat and Rabbit

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The subchronic inhalation toxicology of ethylene glycol monoethyl ether (EGEE) was evaluated in rats and rabbits using a 13-week exposure regimen. Groups of 20 rabbits (10 M, 10 F) and 30 rats (15 M, 15 F) were exposed to a vapor of 25 ppm, 100 ppm, or 400 ppm, 6 hr/day, 5 days/week. The control groups received air only. Physical examinations and body weight measurements were conducted on all animals pretest and weekly throughout the study. Ophthalmoscopic examination was performed pretest and at termination. Evaluation of hematology and clinical chemistry was conducted on 10 animals per sex per group from each species after 13 weeks of study. Histopathological changes were assessed for all animals from the high-dose and control groups. In addition, selected tissues were examined from all animals from the mid- and low-dose groups. Both species exhibited an increased incidence of lacrimation and mucoid nasal discharge, but the response was not consistently dose-related. Rats exposed to EGEE showed no compound-related effects except for a decrease in pituitary to body weight ratio for high-dose males and a decrease in absolute spleen weight for all female animals. The spleen to body weight ratio was also less than controls for the females in the low- and high-dose groups. Pathological changes supportive of these organ weight changes were not observed. The rabbit is the more sensitive species to the subchronic toxicological effects from EGEE. Mean body weight values for low- and high-dose animals were decreased; the mid-dose animals, however, showed no change. Absolute weight and organ to body weight ratio for the testes were decreased for the high-dose group. Microscopic examination of the testes in animals from this group revealed slight focal seminiferous tubule degeneration in 3 out of 10 rabbits. Hematocrit, hemoglobin concentration and erythrocyte count were decreased in the high-dose group of rabbits compared to controls. The level at which no biologically significant effects are observed from subchronic inhalation exposure to EGEE is 400 ppm for rats and 100 ppm for rabbits.

Introduction

Derivatives of ethylene glycol enjoy wide use as solvents in lacquers, enamels, water-based coatings, and wood stains. Other applications include dye solvents in the textile, leather, and printing industries, solvents for insecticides and herbicides, solvents for grease in specialty chemicals, jet-fuel additives, automotive antistall additives, and diluents for hydraulic brake fluids (*1*). Ethylene glycol monomethyl ether (EGEE) is an important derivative of this class of compounds. Its major industrial use is as a solvent for surface coatings such as nitrocellulose lacquers, epoxy coatings, paints, varnishes and varnish removers, and in inks, dyes and hydraulic fluids (*2–4*). In addition, consumer products such as nail enamels and removers, and hair conditioners may contain EGEE (*4*).

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EGEE possesses a low order of toxicity from acute exposure to the adult animal (*5*). The toxicology of EGEE becomes more significant when repeated exposure to adults and exposure to the fetus is considered. Numerous investigators have reported developmental toxicity to the offspring of rats (*6–9*) and rabbits (*6,10*) when exposed *in utero*. Specific organ damage has also been observed in animals treated with this chemical. Nagano et al. (*11*) noted pathological change to the testes and hematological effects in mice exposed orally (5 weeks, 5 days/week) to EGEE at dose levels of 1000 and 2000 mg/kg, respectively.

Testicular effects were observed in rats and dogs following subchronic oral administration (*8*). Short-term exposure to rats has also resulted in testicular toxicity. Foster et al. (*12*) noted depletion of spermatogenesis in rats given EGEE orally for 11 days at a dose of 500 mg/kg.

The present study was undertaken to determine the toxicology of EGEE vapor to rats and rabbits following subchronic inhalation exposure. The rat and rabbit were chosen because these species are sensitive to subchronic

effects from ethylene glycol monomethyl ether (EGME) (*13,14*), a material structurally similar to EGEE.

Materials and Methods

One hundred and twenty Sprague-Dawley CD rats (149 to 275 g) from Charles River Breeding Laboratories (Wilmington, MA) and 80 New Zealand White rabbits (2.1 to 3.3 kg) from Dutchland Laboratories, Inc. (Denver, PA) were used for this study. Animals from each species were divided into three treatment groups and one control group. Each group of rats and rabbits contained 15 and 10 animals per sex, respectively. All animals were housed individually in stainless steel wire mesh cages and maintained in a temperature-, humidity-, and light- (12 hr light/12 hr dark) controlled room during periods of nonexposure. Rats and rabbits were acclimated for 15 and 22 days, respectively. Both species received food and water *ad libitum* except during exposure. Rats received Purina Rodent Laboratory Chow No. 5001, while rabbits were presented with Purina Rabbit Laboratory Chow HF No. 5326.

EGEE (99,59% purity) was supplied by Eastman Chemical Products, Inc. (Kingsport, TN). It was administered via inhalation as a vapor at a concentration of 25, 100 or 400 ppm (92.5, 390, or 1480 mg/m^3) 6 hr/day, 5 days/week for 13 weeks. Control animals received air only under the same conditions as those being treated. All animals were exposed in 10 m^3 stainless steel and glass chambers. During exposure they were housed individually in stainless steel wire mesh cages.

The chambers were operated dynamically at a calibrated airflow rate of approximately 3m^3/min. This flow provided one complete air change approximately every 3 min and a 99% equilibrium time of approximately 15 min.

The test substance was placed in an Erlenmeyer flask for each exposed group and fed through a FMI fluid metering pump and into the liquid end of a 1/4-in. JSS air atomizing nozzle via Teflon tubing and fittings. House line air was delivered into the air end of the atomizer to generate the aerosol. The test atmosphere was directed into the inlet air supply of each chamber. Adjustments in the chamber exposure level were made by adjusting the feed rate of the pump. The nominal chamber concentration was determined by difference. The actual concentration of EGEE in each chamber was obtained using a MIRAN IA General Organic Vapor Analyzer. Samples were collected 6 times per exposure at hourly intervals. Absorbance was read directly from the MIRAN and the concentration of EGEE determined from standard curves. The instrument was calibrated daily prior to exposure.

All animals were observed twice daily for signs of toxicity and morbidity. Individual body weight was recorded weekly. An ophthalmic examination was conducted on all animals during the acclimation period and at the completion of the study.

Clinical laboratory tests were conducted on 10 rats/sex/group and on all rabbits at study termination. Blood was collected from rats via the orbital sinus and from rabbits from the medial ear vein. All animals were fasted overnight prior to collection of blood. The hemato-

Table 1. Body weights of rabbits and rats exposed subchronically to EGEE vapor.[a]

Species	Sex	Week of exposure	Body weight, g			
			0 ppm	25 ppm EGEE	100 ppm EGEE	400 ppm EGEE
Rabbit	M	0	2900 ± 100	2900 ± 100	2900 ± 100	2900 ± 200
		3	3200 ± 200	3100 ± 200	3100 ± 200	3000 ± 100*
		6	3500 ± 200	3400 ± 100	3300 ± 100	3200 ± 200†
		9	3600 ± 200	3500 ± 100	3500 ± 100	3300 ± 200†
		13	3900 ± 300	3700 ± 200*	3800 ± 200	3500 ± 200†
Rabbit	F	0	2400 ± 200	2400 ± 100	2400 ± 200	2400 ± 200
		3	2800 ± 200	2700 ± 200	2900 ± 200	2700 ± 200
		6	3300 ± 200	3000 ± 300	3200 ± 200	2900 ± 400[b]*
		9	3400 ± 300	3200 ± 300[b]	3400 ± 300	3100 ± 300
		13	3800 ± 300	3400 ± 400[b]*	3700 ± 400	3400 ± 300*
Rat	M	0	249 ± 11	254 ± 9	250 ± 10	251 ± 14
		3	358 ± 21	356 ± 19	367 ± 22	365 ± 24
		6	404 ± 36	403 ± 27	423 ± 36	415 ± 27
		9	460 ± 46	453 ± 30	468 ± 44	448 ± 41
		13	475 ± 53[c]	472 ± 38	481 ± 38	471 ± 56
Rat	F	0	171 ± 8	169 ± 6	169 ± 7	170 ± 8
		3	218 ± 11	208 ± 22	210 ± 13	215 ± 8
		6	247 ± 15	253 ± 30	246 ± 20	249 ± 15
		9	264 ± 18	262 ± 18	259 ± 21	270 ± 28
		13	278 ± 23	275 ± 23[c]	267 ± 26	282 ± 38[c]

[a]Each value represents the mean ± SD of data from 10 rabbits and 15 rats unless otherwise noted.
[b]Data for 9 rabbits.
[c]Data for 14 rats.
*$p < 0.05$.
†$p < 0.01$.

logical variables determined were hemoglobin (Hb), hematocrit (Hcrt), erythrocyte count (RBC), reticulocyte count, platelet count, mean corpuscular volume (MCV), hemoglobin (MCH), and hemoglobin concentration (MCHC), total and differential leukocyte counts, and erythrocyte morphology. The clinical chemistry variables determined were aspartate transaminase (AST, EC 2.6.1.1), alanine transaminase (ALT, EC 2.6.1.2), alkaline phosphatase (AP), blood urea nitrogen (BUN), glucose, cholesterol, total protein, albumin, globulin (calculated), albumin/globulin ratio (calculated), creatinine, total bilirubin, direct bilirubin, sodium, potassium, chloride, calcium and inorganic phosphorus. Urinalyses, from rats only, consisted of gross appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood, urobilinogen, and microscopic examination for sediment.

At the completion of the study, all animals were sacrificed by exsanguination under ether anesthesia. A complete necropsy was conducted on all animals on test. Organ weight with calculated organ/body weight ratio was measured for liver, kidneys, testes including epididymides, brain, spleen, thymus, adrenal glands, and pituitary. The following tissues were taken from all necropsied animals and preserved in 10% neutral-buffered formalin: abdominal aorta, adrenals (two), bone marrow (sternum), brain (three sections: including frontal cortex and basal ganglia, parietal cortex and thalmus, cerebellum and pons), eyes (two) with contiguous Harderian gland and optic nerve, gall bladder (rabbit only), gonads (paired ovaries or testes with epididymides), heart, intestine, colon, duodenum, ileum, jejunum, kidneys (two), liver (two sections from separate lobes), lungs with trachea (all lobes of the lung and mainstem bronchi), lymph nodes (mesenteric), mammary gland (right inguinal), nasal turbinates (four sections), pancreas, pituitary, prostate, salivary gland (submandibular), sciatic nerve with muscle, seminal vesicles, skin (flank), spinal cord (cervical and lumbar with vertebrae, spleen, stomach, thymus, thyroid/parathyroid, urinary bladder, uterus (horns and cervix), and vagina. Eyes and testes were placed in Bouin's solution for 48 to 72 hr prior to storage in formalin. Tissues were embedded in paraffin, sectioned and stained with hemotoxylin and eosin. The tissues listed above were examined under light microscopy from

Table 2. Terminal body weights and organ weights of rabbits and rats exposed subchronically to EGEE vapor.[a]

Species	Sex	Exposure concn, ppm	Organ and organ weights					
			Body, g	Adrenals, mg	Testes, g	Brain, g	Pituitary, g	Spleen, g
Rabbit	M	0	3700 ± 300	424 ± 86[b]	8.19 ± 0.82	9.50 ± 0.57		
		25	3500 ± 200*	304 ± 78*	8.73 ± 119	9.50 ± 0.42		
		100	3600 ± 200	364 ± 86	8.73 ± 0.69	9.71 ± 0.35		
		400	3400 ± 200†	351 ± 89	6.36 ± 0.99†	9.29 ± 0.39		
Rabbit	F	0	3700 ± 300[b]	324 ± 79		9.20 ± 0.55		
		25	3300 ± 400*	318 ± 30[b]		9.42 ± 0.37		
		100	3500 ± 300	289 ± 54		9.20 ± 0.48		
		400	3300 ± 300[b]	282 ± 60		9.33 ± 0.39		
Rat	M	0	442 ± 49[c]				10.9 ± 1.4[c]	0.67 ± 0.13[c]
		25	446 ± 34				10.7 ± 1.3	0.68 ± 0.09
		100	454 ± 39				10.2 ± 1.0	0.71 ± 0.11
		400	439 ± 48				9.4 ± 1.0[c]*	0.62 ± 0.08
Rat	F	0	252 ± 23				15.6 ± 2.6	0.52 ± 0.07
		25	253 ± 21[c]				14.5 ± 1.9	0.46 ± 0.05
		100	244 ± 23				13.7 ± 1.7	0.46 ± 0.07*
		400	250 ± 20[c]				14.4 ± 2.8[c]	0.44 ± 0.06[c]†

[a]Each value represents the mean ± SD of data from 10 rabbits and 15 rats unless otherwise noted. Both species fasted overnight prior to sacrifice.
[b]Data from 9 rabbits.
[c]Data from 14 rats.
*$p < 0.05$.
†$p < 0.01$.

Table 3. Hematology data for rabbits exposed subchronically to EGEE vapor.[a]

Variable	Male rabbits, exposure concentration				Female rabbits, exposure concentration			
	0	25 ppm	100 ppm	400 ppm	0	25 ppm	100 ppm	400 ppm
Hb, g/dL	14.6 ± 1.0	14.4 ± 1.2	14.5 ± 0.9	13.0 ± 1.1†	13.9 ± 1.1	14.0 ± 0.6[b]	13.7 ± 0.9	12.8 ± 0.7*
Hcrt, %	41 ± 3	41 ± 3	41 ± 3	37 ± 3*	40 ± 3	41 ± 1[b]	39 ± 2	37 ± 2*
RBC × 10^6/mm^3	6.20 ± 0.58	6.12 ± 0.46	6.03 ± 0.54	5.35 ± 0.53*	5.98 ± 0.48	6.06 ± 0.22[b]	5.94 ± 0.34	5.5 ± 0.33*

[a]Each value represents the mean ± SD of data from 8* or 10 animals unless otherwise noted.
[b]Mean ± SD from 8 animals.
*$p < 0.05$.
†$p < 0.01$.

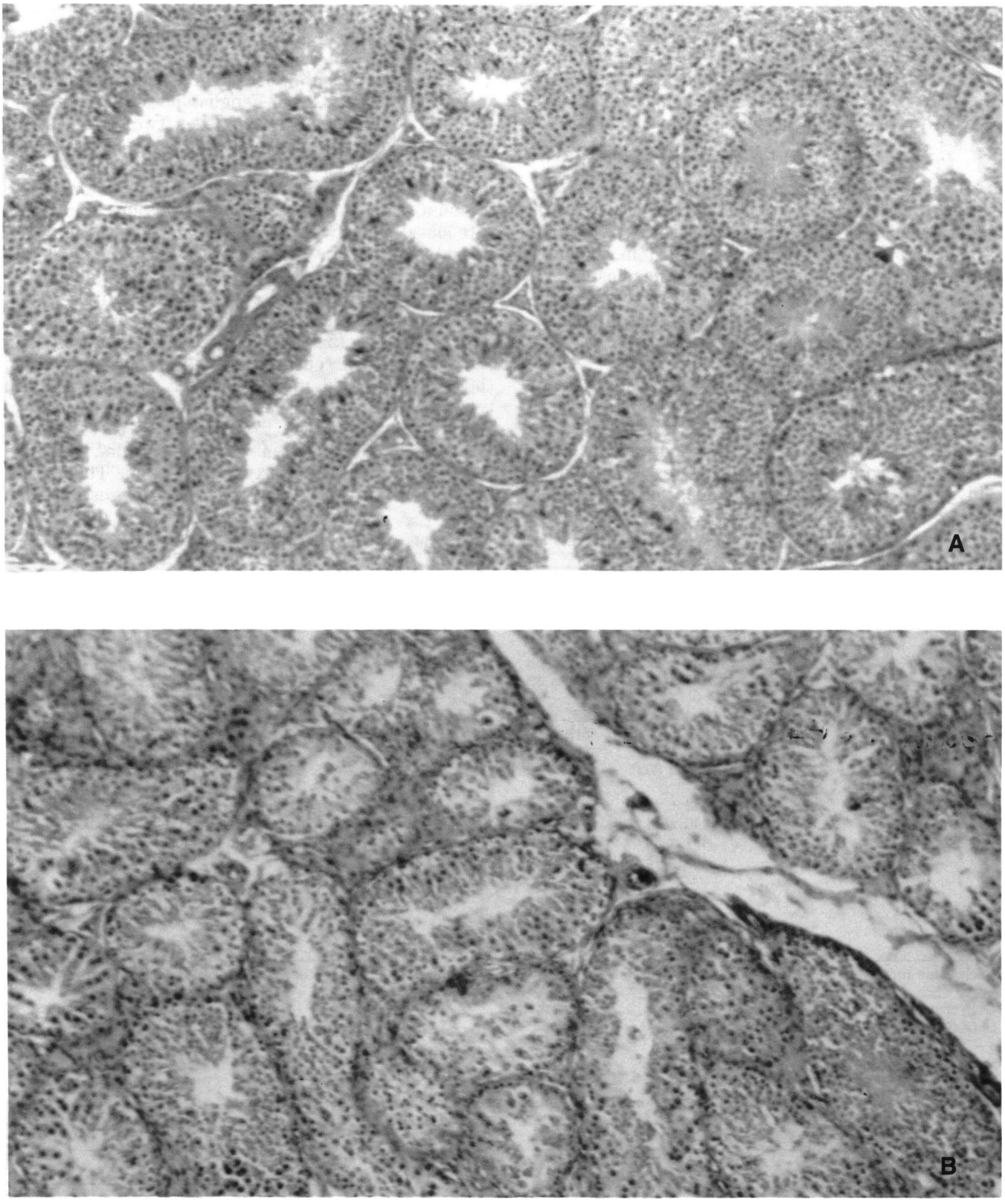

FIGURE 1. Photomicrograph of testicular tissue of the rabbit: (*A*) untreated control rabbits; (*B*) focal degeneration in rabbits exposed to 400 ppm EGEE. Magnification ×40.

all animals in the control and high-concentration groups. In addition, those tissues which are underlined were evaluated from all animals in the mid- and low-concentration groups.

The data were analysed statistically by using tests including Bartlett's test, ANOVA, Dunnett's test, Kruskal-Wallis test, summed rank test (Dunn), regression analysis, and Jonckheere's statistic test.

Results

The daily mean analytical concentration of EGEE for each chamber was within ± 10% of the target concentration except for one day of 19 ppm at the lowest concentration. The overall mean ±SD for the exposure period was 25 ± 1, 103 ± 6, or 403 ± 10 and 25 ± 1, 103 ± 6 or 402 ± 10 for the rats and rabbits, respectively. There was close agreement between the analytical and the nominal concentrations.

An increased incidence of lacrimation and mucoid nasal discharge was observed in all treated groups relative to controls from week 2 through week 10. However, these observations did not occur in a dose-related pattern. The ophthalmoscopic examination revealed no treatment-related effects.

The body weight data are presented in Table 1. The growth of both male and female rabbits was depressed slightly compared to controls although a clear dose response was evident only at 400 ppm. The body weight data for the treated rats were not different significantly from control values. The incidence of organ weight changes in treated relative to control animals was low in both species (Table 2). The adrenal weight from male rabbits was decreased in those animals exposed to 25 ppm EGEE. No change was noted at higher concentrations. The testes weight was decreased significantly in this species at 400 ppm. The relative brain weight of each animal (grams of organ per 100 g of body weight) was increased at all concentrations in female rabbits, but this was due to decreases from controls in terminal body weights. In rats, the only organ weight changes consisted of a decrease in absolute and relative pituitary weight in males exposed to 400 ppm and a decrease in absolute spleen weight at all concentrations in females. The decrease in relative spleen weight was significant only at the low and high concentrations.

The hematological data are shown in Table 3. Male and female rabbits exposed to 400 ppm EGEE sustained decreases in hemoglobin, hematocrit, and erythrocyte count. No hematological changes were observed to either sex at the lower concentrations. The only alteration noted in rats was a drop in leukocyte count from females exposed to 400 ppm. This effect was not seen in males at this concentration and is of unknown biological significance.

Statistically significant differences were observed in serum biochemical variables from both species, but all are of unknown biological significance. Total protein was elevated slightly in male rabbits exposed to 400 ppm. This increase resulted from the globulin fraction. Cholesterol was lowered in females at all concentrations. In rats the only change noted was a depression of blood urea nitrogen in females at the highest concentration.

Data from the urinalyses of rats were unremarkable at all exposure levels.

Gross pathological examination revealed no changes indicative of a treatment-related effect in either species. Evaluation of histopathological change in the rabbit revealed alterations in several tissues. Only the pathological change to the testes appeared related to EGEE exposure. This change to the testes of rabbits is compared in Figure 1. Minimal to slight focal degeneration of seminiferous tubules was noted in three of ten rabbits and was characterized by loss of epithelium. Spermatogenic activity in animals exhibiting histopathologic change, as judged by overall organ morphology, appeared normal.

A variety of incidental microscopic alterations was observed in the tissues examined from both the control and exposed rabbits. In the brain, scattered instances of focal perivascular cuffing and focal encephalitis were seen in both control and exposed rabbits. These inflammatory lesions probably resulted from infection by *Nosema sp.*, even though the organism was not demonstrable with H&E staining. Interstitial lymphoid infiltration and pyelitis, also associated with *Nosema sp.* infection, were seen occasionally in the kidneys from both control and EGEE-treated rabbits. Extramedullary hematopoiesis and pigment deposition were seen consistently in the spleens from both control and exposed rabbits. The severity of these microscopic observations was generally comparable among the control and exposed groups. Pericholangitis and focal necrosis were frequently seen to a minimal to slight degree in the livers from both control and exposed rabbits.

Histopathological evaluation of tissues from the rat revealed no treatment-related lesions. Incidental findings comparable to both control and exposed animals were noted, e.g., extramedullary hematopoiesis, focal pneumonia, focal aveolitis, and focal bronchitis. Histopathological lesions supportive of organ weight changes for the spleen and pituitary gland were not observed.

Discussion

The results from this study indicate that the rabbit is the more sensitive species to subchronic exposure to EGEE vapor. Data from body weight, organ weight (males only), hematology and pathological change (males only) support a dose-related effect to both sexes of this animal exposed to 400 ppm. Animals at this concentration gained weight steadily, but lagged the control group. They also showed evidence of anemia and testicular changes characterized by degeneration of tubular epithelium. Although isolated statistically significant

changes from control values occurred on all concentrations in rats, none was judged treatment-related.

The anemia observed in rabbits appears to be the result of an increase in the destruction of erythrocytes rather than a depression of erythropoiesis. No pathological change to the bone marrow was noted. The hematologic data suggest that the remaining cells are normal since no change from control values was observed in MCH, MCV, or MCHC.

Nagano et al. (*10*) noted testicular and hematologic changes in mice exposed orally to EGEE. The testicular changes (decrease in weight and atrophy) were observed at a threshold of 1000 mg/kg while effects to the blood (decrease in white blood cell count) were not seen until 2000 mg/kg. The threshold dose at which these effects occurred was significantly higher than the dose received by rabbits in this study based on physiological data developed by Guyton (*13*). If we assume complete retention of the inhaled EGEE by rabbits, the daily dose received at the observed no-effect level (ONEL) would be approximately 50 mg/kg/day compared to the ONEL of 500 mg/kg/day for mice in the Nagano (*10*) work. Again the rabbit appears to be the more sensitive species.

The mechanism of testicular toxicity in rats produced by EGEE has been investigated by Foster et al. (*12*). They found that degeneration in this organ was restricted to the later stages of primary spermatocyte development and secondary spermatocytes. Sertoli and Leydig cells, spermatogonia, prepachytene spermatocytes, and spermatids were unaffected apart from partial maturation depletion of early stage spermatids. These authors also treated rats with equimolar doses of 2-ethoxyacetic acid (2-EAA), an EGEE metabolite. The testicular lesions produced by 2-EAA were similar qualitatively and quantitatively to those produced by EGEE, indicating that the toxicity of EGEE may be due to formation of this metabolite.

The inhalation toxicology from repeated exposure has been studied using EGME. Doe et al. (*14*) exposed rats to 100 or 300 ppm EGME 6 hr/day for 10 days. At 300 ppm, a reduction in testicular weight and atrophy of the seminiferous tubules were noted. Exposure to this concentration also produced decreases in red and white blood cell counts, Hb, Hcrt, and MCH. Miller et al. (*15*) exposed rats and mice to 100, 300 or 1000 ppm EGME vapor for 6 hr/day for 9 days. Rats exposed to 1000 ppm EGME showed body and organ weight changes, anemia and pathological change to the testes, bone marrow, thymus, spleen, and mesenteric lymph nodes. In a follow-up investigation (*16*), rats and rabbits exposed subchronically (6 hr/day, 5 days/week for 13 weeks) to 30, 100 or 300 ppm EGME vapor also sustained target organ damage. Although rats were affected only at 300 ppm, changes suggestive of a treatment-related effect to the testes occurred at 30 ppm in rabbits. Foster et al. (*12*) compared EGME-mediated testicular effects to those produced by EGEE in the rat. EGME produced damage similar to that from EGEE, but a lower dose was necessary to produce comparable pathological change. Effects to this organ were observed from daily exposure to EGME for 11 days at a dose of 100 mg/kg, while 500 mg/kg of EGEE was necessary to produce similar changes. 2-Methoxyacetic acid elicited lesions equivalent to EGME at equimolar doses. Rao et al. (*17*) noted impaired reproductive capability in male but not in female rats exposed subchronically to 300 ppm EGME.

The testicular effects from EGEE in rabbits were noted in a minority (3/10) high exposure of animals. These were judged to be minimal to slight. The anemia also appears to be slight. The changes from EGEE are similar qualitatively to those produced by EGME. However, EGEE is clearly less potent. The ONEL from subchronic inhalation of EGEE vapor is 400 ppm in rats and 100 ppm in rabbits.

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